UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

July 2, 1998

MEMORANDUM

SUBJECT: Review of Diazinon Incident Reports
DP Barcode D245285, Chemical #057801, Reregistration Case #0238

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I. INTRODUCTION

Diazinon is an organophosphate insecticide widely used in the United States. As a result of this widespread use, there have been numerous exposures and poisonings. Detailed analysis of the incident data identified specific use patterns that are more likely to be associated with pesticide poisoning. Depending on the type of use, risk mitigation measures are recommended to reduce the associated types of poisoning. In addition to acute poisoning, diazinon and other organophosphate insecticides have been reported to be associated with chronic effects in humans, including peripheral neuropathy, chronic neurobehavioral effects, and the reported development of a sensitivity to chemicals previously tolerated which is associated with a wide variety of symptoms. Evidence for these effects is also reviewed.

The purpose of this document is to summarize the case reports, case series, statistical surveys, and epidemiologic studies of acute and chronic health effects reported to be related to diazinon. By its nature, such information suffers a number of limitations including inadequate documentation of exposure and effects, reporting biases, and absence of denominator information on the population at risk. Where consistent patterns of risk factors are identified, it is also the purpose of this document to recommend measures to mitigate those risks. To facilitate the reader's review the following listing of contents is provided:

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Diazinon is a member of the class of organophosphate (OPs) insecticides. The organophosphate insecticides are among the most widely used agents for control of insects in agricultural and residential settings. Close to 40 organophosphates (OPs) are currently registered with the U. S. Environmental Protection Agency (EPA) and used in the United States with a widely varying range of acute toxicity.

Diazinon and the other OPs poison humans and insects through their effects on nerve enzymes (Morgan 1989). Diazinon combines chemically with the acetylcholinesterase enzyme and inactivates it. This enzyme is essential for control of nerve impulse transmission. Loss of acetylcholinesterase allows the accumulation of acetylcholine, the substance secreted by nerves that activates muscles, glands, and other nerves (Morgan 1989). Accumulation of sufficient levels of acetylcholine at junctions between nerves and muscles will cause muscle contractions or twitching. Accumulation of acetylcholine at junctions between nerves and glands results in gland secretion. And accumulation of acetylcholine between nerves

in the brain will result in sensory and behavioral disturbances.

The principal signs and symptoms of acute diazinon poisoning are headache, nausea, dizziness, pinpoint pupils, blurred vision, hypersecretion, tightness in chest, difficulty breathing, muscle weakness or twitching, difficulty walking, vomiting, abdominal cramping, and diarrhea (Namba 1971; World Health Organization 1986; Minton and Murray 1988; Karalliedde and Senanayake 1989; Morgan 1989; Gallo and Lawryk 1991). Hypersecretion of glands often results in profuse sweating and salivation, as well as tearing, runny nose, and bronchial secretions. Effects to the central nervous system may include confusion, anxiety, drowsiness, depression, difficulty concentrating, slurred speech, poor recall, insomnia, nightmares, emotional lability, or a form of toxic psychosis resulting in bizarre behavior. In any one poisoning episode, varying combinations of these symptoms may occur at different times after exposure, varying from a few minutes to several hours. The number of symptoms present also varies depending on the dose and mode of exposure. According to Morgan, unconsciousness (coma), incontinence, convulsions, or depression of respiratory drive are evidence that the poisoning is life-threatening (Morgan 1989). Pulmonary edema (fluid in the lungs), marked miosis (pinpoint pupils) with loss of pupillary reflex, loss of reflexes and extreme muscle weakness (flaccid paralysis), ataxia (jerky movements), slurring or repetitive speech are also signs of severe, life-threatening poisoning (Namba et al. 1971; Eskenazi and Maizlish 1988; Minton and Murray 1988; Gallo and Lawryk 1991).

Poisoning due to unrecognized dermal absorption (as well as other routes of exposure) can be easily misdiagnosed, which suggests that some individual cases of poisoning are missed (Midtling et al. 1985; Coye et al. 1986). Table 1 lists symptoms and signs commonly associated with acute organophosphate insecticide poisoning. These symptoms were selected based on a review of the literature (Morgan 1989, Minton and Murray 1988, Gallo and Lawryk 1991, Namba et al. 1971).

Table 1. Examples of symptoms and signs that may be reported in acute organophosphate insecticide poisoning. Note that the presence of one or more of these symptoms can occur from other diseases and differential diagnosis by a physician is needed.

Common early or mild signs/symptoms	Present in moderate or severe poisoning	Presence signifying life-threatening severity

Headache Nausea/Vomiting Dizziness Muscle weakness Drowsiness/lethargy Agitated/anxiety	Tightness in chest Difficult breathing Bradycardia* Tachycardia Hypertension Hypotension Pallor/cyanosis Abdominal pain Diarrhea Anorexia Tremor/Ataxia Fasciculations* Lacrimation* Heavy salivation* Profuse sweating* Bronchorrhea* Blurred vision Pinpoint pupils* Poor concentration Confusion/delusions Memory loss	Coma Seizures Incontinence Respiratory arrest Pulmonary edema Loss of reflexes Flaccid paralysis

* Presence of these signs and symptoms are considered relatively specific for organophosphate insecticide poisoning (Morgan 1989, O'Malley 1992).

II. BACKGROUND

The following data bases have been consulted for the poisoning incident data on the active ingredient Diazinon (PC Code: 057801):

1) Incident Data System (IDS) - reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to the Office of Pesticide Programs (OPP) since 1992. Reports submitted to the Incident Data System represent anecdotal reports or allegations only, unless otherwise stated. Typically no conclusions can be drawn implicating the pesticide as a cause of any of the reported health effects. Nevertheless, sometimes with enough cases and/or enough documentation, risk mitigation measures may be suggested.

2) Poison Control Centers - as the result of Data-Call-Ins issued in 1993, OPP received Poison Control Center data covering the years 1985 through 1992 for 28 organophosphate and carbamate chemicals. Most of the national Poison Control Centers (PCCs) participate in a national data collection system, the Toxic Exposure Surveillance

System which obtains data from about 65 centers at hospitals and universities. PCCs provide telephone consultation for individuals and health care providers on suspected poisonings, involving drugs, household products, pesticides, etc.

3) California Department of Food and Agriculture (replaced by the Department of Pesticide Regulation in 1991) - California has collected uniform data on suspected pesticide poisonings since 1982. Physicians are required, by statute, to report to their local health officer all occurrences of illness suspected of being related to exposure to pesticides. The majority of the incidents involve workers. Information on exposure (worker activity), type of illness (systemic, eye, skin, eye/skin and respiratory), likelihood of a causal relationship, and number of days off work and in the hospital are provided.

4) National Pesticide Telecommunications Network (NPTN) - NPTN is a toll-free information service supported by OPP. A ranking of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991, inclusive has been prepared. The total number of calls was tabulated for the categories human incidents, animal incidents, calls for information, and others.

III. INCIDENT DATA SYSTEM

Please note that the following cases from the IDS do not have documentation confirming exposure or health effects unless otherwise noted. A small number of cases reported by United Industries Corporation involving only minor effects have not been included in this summary. The data reported from these cases did not include enough information to provide useful information.

Incident#244-1

A pesticide incident occurred in 1992, when several applicators applied diazinon to lawns and experienced nausea, headaches, and hunger pains. The applicators may have also mixed the chemicals used for the spraying. After the spraying, one resident experienced difficulty breathing and was hospitalized. An investigation of these cases suggested the following risk factors: heat and fatigue, wearing clothing wet with spray, not using gloves and boots as required by the lawn care company management, and the odor from solvents and emulsifiers. None of these cases were seen by a doctor or had cholinesterase measurements taken. No further information on the disposition of the case was reported.

Incident#249-1

Lawsuit with no specific symptoms mentioned.

Incident#264-1

A pesticide incident occurred in 1985, when a thirty-nine year old man, who was taking a prescription drug Tagamet, had his lawn treated with diazinon two days earlier and later experienced cancer, brain damage, peripheral nerve damage, injury to the central nervous system, eyesight damage, profuse rhinorrhea, and several other symptoms. Though interaction with the drug Tagamet was suggested, it was never confirmed. See the literature section for further discussion on this case.

Incident#444-15

PCO inhaled dust during application and not feeling well. No specific symptoms were mentioned.

Incident#512-1

Attempted suicide involving alcohol and injection of diazinon in an adult female was reported. Symptoms and outcome of this case were not reported.

Incident#764-1

Attempted suicide reported in a 34 year old male who ingested about one ounce of product containing 87% diazinon. Nausea and vomiting were reported and the patient recovered with treatment. Other symptoms may also have occurred but were not reported.

Incident#771-1

A pesticide incident occurred in 1993, when a woman was working in a house that had been treated with diazinon three days earlier and experienced severe sweating, weakness, vision problems, memory loss, and incoordination and still experiences the sweating, memory loss, and muscle control difficulties. No further information on the disposition of the case was reported.

Incident#842-1

A pesticide incident occurred in 1994, when a man was cleaning up a diazinon product that had ruptured and experienced headaches. No further information on the disposition of the case was reported.

Incident#844-38

In 1993, occupants of a court house complained of not feeling well after the attic and grounds surrounding a building were treated with diazinon. No further information on the disposition of the case was reported.

Incident#850-1

A pesticide incident occurred in 1989, when diazinon was applied in a school and a teacher and students experienced headaches, nausea, difficulty breathing, abdominal pain, and eye irritation. The teacher developed multiple chemical sensitivity and is permanently disabled. No further information on the

disposition of the case was reported.

Incident#859-1

A summary of container rupture from 1977 through January 1994 listed 334 incidents of which 36 involved reports of health effects. Nausea, headache, and sore throat were the most common symptoms reported. Seven of the cases had cholinesterase measurements taken which were normal. No further information on the disposition of these cases was reported.

Incident#941-31

A pesticide incident occurred in 1994, when an individual experienced dermal itching. No further information on the disposition of the case was reported.

Incident#941-42

A pesticide incident occurred in 1994, when an individual experienced ocular irritation and pain. No further information on the disposition of the case was reported.

Incident#941-60

A pesticide incident occurred in 1994, when an individual experienced a dermal rash. No further information on the disposition of the case was reported.

Incident#941-68

A pesticide incident occurred in 1994, when an individual experienced drowsiness and lethargy. No further information on the disposition of the case was reported.

Incident#975-16

A pesticide incident occurred in 1994, when an individual experienced ocular irritation and pain and throat irritation. No further information on the disposition of the case was reported.

Incident#975-19

A pesticide incident occurred in 1994, when an individual experienced gastrointestinal symptoms. No further information on the disposition of the case was reported.

Incident#975-26

A pesticide incident occurred in 1994, when an individual experienced dermal irritation and pain. No further information on the disposition of the case was reported.

Incident#975-32

A pesticide incident occurred in 1994, when an individual experienced ocular irritation and pain. No further information on the disposition of the case was reported.

Incident#975-36
A pesticide incident occurred in 1994, when an individual experienced a dermal rash. No further information on the disposition of the case was reported.

Incident#975-40
A pesticide incident occurred in 1994, when an individual experienced respiratory symptoms. No further information on the disposition of the case was reported.

Incident#975-45
A pesticide incident occurred in 1994, when an individual experienced dermal symptoms. No further information on the disposition of the case was reported.

Incident#975-46
A pesticide incident occurred in 1994, when an individual experienced vomiting. No further information on the disposition of the case was reported.

Incident#999-10
A pesticide incident occurred in 1994, when an individual experienced itching and fasciculations. No further information on the disposition of the case was reported.

Incident#999-18
A pesticide incident occurred in 1994, when an individual experienced tachycardia. No further information on the disposition of the case was reported.

Incident#999-23
A pesticide incident occurred in 1994, when an individual experienced ocular irritation and pain and fasciculations. No further information on the disposition of the case was reported.

Incident#999-25
A pesticide incident occurred in 1994, when an individual experienced coughing, choking, and dystonia. No further information on the disposition of the case was reported.

Incident#999-44
A pesticide incident occurred in 1994, when an individual experienced fasciculations and respiratory symptoms (not specified). No further information on the disposition of the case was reported.

Incident#999-54
A pesticide incident occurred in 1994, when an individual experienced nausea, vomiting, and fasciculations. No further

information on the disposition of the case was reported.

Incident#999-56

A pesticide incident occurred in 1994, when an individual experienced ocular irritation and pain, hallucinations, and delusions. No further information on the disposition of the case was reported.

Incident#999-61

A pesticide incident occurred in 1994, when an individual experienced a dermal rash. No further information on the disposition of the case was reported.

Incident#999-74

A pesticide incident occurred in 1994, when an individual experienced fasciculations and difficulty breathing. No further information on the disposition of the case was reported.

Incident#999-93

A pesticide incident occurred in 1994, when an individual experienced nausea. No further information on the disposition of the case was reported.

Incident#999-139

A pesticide incident occurred in 1994, when an individual experienced drowsiness, lethargy, and muscle weakness. No further information on the disposition of the case was reported.

Incident#999-140

A pesticide incident occurred in 1994, when an individual experienced nausea, drowsiness, and lethargy. No further information on the disposition of the case was reported.

Incident#1057-1

A pesticide incident occurred in 1994, when an individual applied diazinon with a drop spreader and experienced chills, headaches, weakness, and a swollen hand. No further information on the disposition of the case was reported.

Incident#1125-8

A pesticide incident occurred in 1994, when an individual, who was hospitalized for four days, experienced nausea, shortness of breath, lightheadedness, muscle twitching, stomach pains, and diarrhea. No further information on the disposition of the case was reported.

Incident#1258-1

A pesticide incident occurred in 1984, when a woman treated

her lawn with diazinon using a hand held rotary spreader and experienced coughing. No further information on the disposition of the case was reported.

Incident#1259-1

A pesticide incident occurred in 1994, when a seventy year old man applied diazinon and three days later experienced burning and puffy eyes, burning lips, and shortness of breath. No further information on the disposition of the case was reported.

Incident#1329-1

Attempted suicide was reported involving ingestion of one pint of an unknown formulation. Specific symptoms were not mentioned. No further information on the disposition of the case was reported.

Incident#1358-1

A total of 62 incidents related to diazinon were reported in summary form from Poison Control Center data for August 1994. The majority of cases, 57 or 92% had a minor outcome, typically with dermal or eye irritation or pain, rash, nausea, vomiting, headache, or dizziness. Two cases reported moderate effects with similar symptoms. There were three cases with major or life threatening effects including tachycardia (all 3), pulmonary edema (2 cases), and seizure (2 cases). All three major cases resulted from ingestion of products containing 25% diazinon. No further information on the disposition of the case was reported.

Incident#1360-2

In a lawsuit, the plaintiff experienced severe damage to the central nervous system. He was exposed when ordered to clean up a misapplication of diazinon that had not been diluted with 50 parts water per part insecticide concentrate as required by the label. Symptoms reported in hospital records included miosis (pinpoint pupils), muscle twitching, muscle weakness, along with other unspecified symptoms. Cholinesterase testing revealed below normal levels in the blood. Chronic problems reported after this incident included eye problems, difficulty sleeping, depression, anxiety, memory problems, headaches, muscle weakness, high blood pressure, and gastrointestinal problems. Expert testimony differed as to whether these effects were or were not due to the diazinon exposure.

Incident#1669-1

Adult male attempted suicide by drinking 8 ounces of an unspecified formulation. He was treated in a hospital but specific symptoms not mentioned. No further information on the disposition of the case was reported.

Incident#1797-1

Adult female sprayed diazinon on numerous occasions and got it on her hands without washing it off immediately. She reported having difficulty walking to the point of using a wheel chair, but has since recovered. She also reports allergies and fibromyalgia. No medical documentation is provided in this anecdotal report.

Incident#1911-4

A pesticide incident occurred in 1994, when a man used a spray can and collapsed about ten or fifteen minutes later. Eight weeks later he alleged he was unable to engage in normal activities due to his exposure. No further information on the disposition of the case was reported.

Incident#2002-1

A pesticide incident occurred in 1995, when a woman was exposed to diazinon that was used to treat anthills that drifted nearby onto plum trees. The woman ate some of the plums and experienced blurred vision, headaches, vomiting, diarrhea, and a low blood potassium level. No further information on the disposition of the case was reported.

Incident#2178-1

A pesticide incident occurred in 1995, when a woman’s office was sprayed for termites and experienced nausea, vomiting, abdominal pain, diarrhea, and headaches. No further information on the disposition of the case was reported.

Incident#2284-1

In a lawsuit, the plaintiff experienced nausea, dizziness, vomiting, fevers, sweating, chills, coughing, and slurred speech. No further information is available on the disposition of this case.

Incident#2323-1

A pesticide incident occurred in 1995, when fourteen workers reentered a building that was sprayed over the weekend. The building had been sprayed at 16 times the recommended level. The workers experienced nausea, lightheadedness, dizziness, dry mouth, and disorientation. No further information on the disposition of the case was reported.

Incident#2341-1

A pesticide incident occurred in 1995, when a woman experienced swollen legs and knots on the legs. No further information on the disposition of the case was reported.

Incident#2342-2

A pesticide incident occurred in 1995, when a woman and her

husband experienced dizziness after their lawn was treated the previous day with diazinon. No further information on the disposition of the case was reported.

Incident#2398-1

A case series is reported including one male in his 30s exposed only to diazinon. He reportedly experienced memory loss, headache, dizziness, nausea, and unspecified chest and heart problems. No further information on the disposition of the case was reported.

Incident#2467-1

A pesticide incident occurred in 1995, when a female in her early twenties attempted suicide by ingesting four ounces of diazinon. She experienced lethargy, constricted pupils, tachycardia, and nausea. No further information on the disposition of the case was reported.

Incident#2512-8

A pesticide incident occurred in 1995, when a woman treated her yard and house for two days using a hand applicator and was hospitalized for five days. She experienced dizziness, blurred vision, and headaches. Use of safety equipment or precautions was questioned by the state investigators. No further information on the disposition of the case was reported.

Incident#2576-2

A pesticide incident occurred in 1995, when a man attempted suicide by ingesting 25% of a one pint bottle of diazinon and was hospitalized for three days. He experienced lethargy and bowel and bladder incontinence (considered a life-threatening sign, Morgan 1989). Given that one pint holds approximately 454 grams (assuming specific gravity = 1 mg/mL) then this man would have ingested (.25 x 454) 113 grams or a dose of about 405 mg/kg (assuming body weight of 70 kg and a 25% formulation) in this life-threatening poisoning. No further information on the disposition of the case was reported.

Incident#2630-1

A pesticide incident occurred in 1995, when a landfill inspector and another individual were exposed to diazinon that was unloaded off a sanitation truck. They experienced hives and blisters on their skin. No further information on the disposition of the case was reported.

Incident#2631-1

A pesticide incident occurred in 1995, when a man emptied diazinon into a fertilizer spreader and experienced hives from his neck down to his feet and difficulty breathing. No further information on the disposition of the case was reported.

Incident#2800-3
A pesticide incident occurred in 1995, when a boy's bed was inadvertently sprayed with undiluted diazinon. Specific symptoms were not mentioned. No further information on the disposition of the case was reported.

Incident#2908-1
A pesticide incident occurred in 1995, when a truck driver was exposed to an eight ounce package of diazinon that spilled in his truck. He experienced headaches and nausea. No further information on the disposition of the case was reported.

Incident#2954-1
A pesticide incident occurred in 1995, when a farmer was taken to the hospital with severe acute pancreatitis and died five days later. No further information on the disposition of the case was reported.

Incident#3037-106
A pesticide incident occurred in 1994, when an individual attempted suicide or accidentally ingested one gallon of diazinon and tralomethrin. This person experienced convulsions and unconsciousness. No further information on the disposition of the case was reported.

Incident#3249-4
A pesticide incident occurred in 1996, when a sixty-seven year old man attempted suicide by ingesting four ounces of diazinon (formulation unknown) and was hospitalized for two days. He experienced stomach aches, nausea, vomiting, flushed feeling, and lethargy. Cholinesterase levels were depressed. No further information on the disposition of the case was reported.

Incident#3249-18
A pesticide incident occurred in 1996, when a thirty-nine year old woman attempted suicide and was hospitalized for ten days. Specific symptoms were not mentioned. No further information on the disposition of the case was reported.

Incident#3263-10
A pesticide incident occurred in 1996, when a one month old infant was hospitalized for four days after their home was treated for cockroaches. The infant experienced lethargy, vomiting, diarrhea, and foaming of the mouth. No further information on the disposition of the case was reported.

Incident#3263-15
A pesticide incident occurred in 1996, when a forty-one year old woman sprayed the exterior of her home for fleas and

experienced weakness, rapid heart rate, dizziness, difficulty breathing, blurred vision, headaches, and numbness in the hands and arms. She was hospitalized for four days. No further information on the disposition of the case was reported.

Incident#3470-3
Lawsuit with a variety of vague symptoms.

Incident#3470-4
Lawsuit with a variety of vague symptoms.

Incident#3471-1
In a lawsuit, a family alleged they experienced headaches, nausea, vomiting, congestion, and drowsiness. No further information is available of the disposition of this case.

Incident#3471-2
Lawsuit with vague symptoms.

Incident#3471-4
Lawsuit with vague symptoms.

Incident#3471-5
Lawsuit with vague symptoms.

Incident#3471-6
Lawsuit with vague symptoms.

Incident#3471-7
Lawsuit with vague symptoms.

Incident#3471-9
Lawsuit with vague symptoms.

Incident#3471-10
Lawsuit with vague symptoms.

Incident#3480-2
A pesticide incident occurred in 1996, when twenty-two people sought medical attention after exposure to diazinon when a building was treated with the chemical. One person experienced facial tingling and vomiting. No further information on the disposition of the case was reported.

Incident#3480-4

A pesticide incident occurred in 1996, when several hospital staff experienced dizziness, headaches, and eye irritation. The

staff experienced the symptoms after a patient was brought to the emergency room who was experiencing vomiting and had stopped breathing after an ingestion. No further information on the disposition of the case was reported.

Incident#3480-5

A pesticide incident occurred in 1996, when a thirty-seven year old woman ingested three ounces of diazinon and was hospitalized for an unknown amount of days. She experienced vomiting, involuntary urination and defecation (life-threatening symptoms, see Morgan 1989), lacrimation, and confusion. Had this been 25% diazinon (the formulation was not specified), the highest percent formulation commonly available to the public, she would have ingested approximately 21.3 grams. Assuming a weight of 60 kg, her dose would have been 355 mg/kg in this life-threatening poisoning. No further information on the disposition of the case was reported.

Incident#3480-12

A pesticide incident occurred in 1995, when a man treated his house and kept the windows closed for the next three to four hours. The windows were opened for about an hour before he and his family reentered the house. His thirty-six year old wife, who was five months pregnant, experienced nausea, vomiting, headaches, decreased appetite, decreased energy, and dehydration. She was hospitalized overnight and released the next day. No further information on the disposition of the case was reported.

Incident#3553-1

In a lawsuit, the plaintiff experienced chest pain, asthma, breathing problems, headaches, extreme fatigue, muscle pain, rashes, and several other symptoms. No further information on the disposition of the case was reported.

Incident#3599-1

The Minnesota Department of Agriculture surveyed state enforcement agencies to determine what pesticides were involved in spray drift. Among the thirty-two states responding to the survey, there was a total of 2,681 cases of drift complaints. Diazinon was responsible for 6 complaints or less than one percent of the total.

Incident#3698-1

A pesticide incident occurred in 1996, when an individual poured diazinon into a crack in the garage near the air conditioning unit. They experienced a burning sensation, dizziness, and confusion. No further information on the disposition of the case was reported.

Incident#3998-1

A pesticide incident occurred in 1996, when a man and his wife spread diazinon in their basement and left the house for a vacation. After returning three weeks later, the wife experienced nausea, headaches, and wheezing. No further information on the disposition of the case was reported.

Incident#4104-1

A pesticide incident occurred in 1992. Three years later a man contacted EPA and complained of lack of concentration, incoordination, depression, memory and eye problems, and inability to pick up items and walk. He believes these persistent symptoms are due to the initial diazinon exposure. No further information on the disposition of the case was reported.

Incident#4191-1

A pesticide incident occurred in 1996, when a woman experienced nausea, dizziness, and physical depression after her lawn was treated with diazinon. No further information on the disposition of the case was reported.

Incident#4533-5

A pesticide incident occurred in 1996, when a man sprayed for ants in his backyard with diazinon which blew in his face. He experienced shortness of breath and developed dry heaves. He went to the hospital and received treatment for two days. No further information on the disposition of the case was reported.

Incident#4697-

Listed below are categories of symptoms for 48 incidents that are involved in lawsuits:
Nonspecific-5
Acute poisoning-25 (some had acute effects that persisted)
Chronic symptoms-8
Reproductive-4
Cancer and precursors-4
Chronic neurological/psychological-2
Death-1

Incident#4869-2

A pesticide incident occurred in 1996, when several workers were exposed to diazinon, copper hydroxide, and petroleum oil that were applied to an adjacent orchard. The workers experienced headaches, nausea, and vomiting. No further information on the disposition of the case was reported.

Incident#5005-1

Lawsuit with vague symptoms.

Incident#5142-1

A pesticide incident occurred in 1997, when a six year old girl had her hair washed for head lice by her mother's boyfriend with diazinon. She was hospitalized for an unknown amount of time after experiencing a full cardiac and respiratory arrest. No further information on the disposition of the case was reported.

Incident#5895

Listed below are categories of symptoms for 150 incidents that are involved in lawsuits:

Nonspecific-13
Acute poisoning-123 (many with persistent symptoms)
Chronic symptoms-12
Reproductive-0
Cancer and precursors-1
Chronic neurological/psychological-1
Death-0

Incident#6250-1

A pesticide incident occurred in 1997, when students and teachers at an elementary school complained of odor and feeling ill after diazinon was applied to bushes and shrubbery around the school. No further information on the disposition of the case was reported.

Incident#6252-1

A pesticide incident occurred in 1997, when an eighty-five year old woman committed suicide by ingesting diazinon and died four days later. A brain tumor may have been a contributing factor in this case. No further information on the disposition of the case was reported.

Incident#6282-4

A pesticide incident occurred in 1997, when the owner of a cat that wore a collar with diazinon experienced headaches. No further information on the disposition of the case was reported.

Incident#6284-1

A pesticide incident occurred in 1997, when a woman had her home treated with diazinon and reentered her house about six hours later. She experienced shortness of breath, nausea, and tingling in her hands. No further information on the disposition of the case was reported.

As stated before, the majority of cases had insufficient documentation of exposure and effects. Therefore, individually they do not provide much evidence. However, when the overall

pattern of problems is documented in other independently collected data of higher quality, the data can help identify use patterns amenable to risk mitigation. Among the problems identified in the incident data which will be corroborated with other data sources were chronic neurobehavioral effects (e.g., I#771-1, I#1360-2, I#4104-1), cluster poisonings involving several victims exposed to residue from an indoor application (e.g., I#850-1, I#2323-1, I#3480-2), serious illness due to improper dilution (e.g., I#1360-2, I#2323-1, I#2800-3), serious illness in hand applicators who were inadequately protected (e.g., I#2512-8), and the potential for dermal exposure to be life-threatening (e.g., I#5142-1). In two nearly-fatal cases of ingestion, the volume ingested permits estimating the potentially lethal dose for humans. Potential lethal doses were estimated to be 405 mg/kg (I#2576-2) and 354 mg/kg (I#3480-5).

IV. POISON CONTROL CENTER DATA - 1985-1992

This section describes Poison Controls Centers operation and their nationwide system of data collection. The use of a standardized form for data collection, definition of key data elements, and quality assurance procedures are outlined.

Starting in 1984 the American Association of Poison Control Centers (AAPCC) made available a computerized system to collect data on all poison exposures reported to the Poison Control Centers (PCCs) nationwide (Litovitz and Veltri 1985). The system had been piloted in 1983 (Veltri and Litovitz 1984).

Poison Centers receive telephone calls from individuals and health care providers seeking information on how to manage an exposure to a poison. Typically the Poison Center itself is run by a hospital or university. "Poison Centers function primarily to provide poison information, telephone management and consultation, collect pertinent data, and deliver professional and public

information" (AAPCC 1988). Each center must have a poison information specialist available on site at all times. Written operational guidelines must be used to assure a consistent approach to the handling of all poison exposures. Included in the guidelines must be provision for follow-up of each case to determine patient's final disposition or medical outcome.

The Poison Centers participating in the Toxic Exposure Surveillance System (formerly the National Data Collection System) complete a form or computer record describing each case that contains standard data elements and a narrative section. Information collected includes the date of call, age and sex of the victim, location of victim at time of exposure (e.g., home, work place), substance, route of exposure, initial symptom assessment, treatment received (e.g., referred to physician, hospitalized), and medical outcome. Starting in 1993 information about specific symptoms reported was also collected. Data from the form are then sent to the AAPCC for processing. A computer record is prepared and returned to the local centers (AAPCC 1988).

Patients treated at home or any other non-health care site are classified as "managed on site" (Interpretation of the AAPCC Data, AAPCC 1987). Those seen in a health care facility may be classified as either treated and released or admitted for medical care. "Admitted for medical care" is used when "the patient is observed and/or treated and subsequently admitted as an inpatient primarily to receive medical care rather than psychiatric evaluation".

When symptoms occur they are categorized into minor, moderate, or major depending on their severity and whether recovery is complete. Definitions used by the Poison Control Centers to categorize medical outcome are given in summary form below (Veltri et al. 1987).

Minor: Minimal symptoms with no residual disability (e.g., mild gastrointestinal symptoms, skin irritation, drowsiness).

Moderate: Symptoms are more pronounced, prolonged, or more of a systemic nature than minor symptoms with no residual disability. Usually some form of treatment is indicated. Examples include: high fever, disorientation, hypotension which rapidly responds to treatment and isolated brief seizures.

Major: Symptoms are life-threatening or result in residual disability or disfigurement. Examples include patients who require intubation plus mechanical ventilation, who sustain repeated seizures, cardiovascular instability, or

coma.

Poison Centers collect data on each call they receive and transfer the information to the Toxic Exposure Surveillance System. Many poisoning cases seen in emergency rooms or by private physicians do not result in calls to a PCC. A study of all acute care hospitals in Utah compared all inpatient and outpatient records of poisoning with calls to the Poison Center serving Utah and found that only about one-third of the cases matched (Veltri et al. 1987). Characteristics of unmatched cases were not studied so it is not possible to say how PCC cases might differ from hospital cases that do not result in a call to a PCC. All Poison Centers supplying data to the Toxic Exposure Surveillance System must be certified, which means that certain quality assurance procedures for the data collection must be in place.

Validity of the data collected by different poison centers is an important concern of the Toxic Exposure Surveillance System. Some 65 Centers staffed by five or more personnel each are responsible for collection of the information on each case, properly coding the information and submitting it to the AAPCC which maintains the national database. Reporting by individual PCCs is dependent on how well their service is known and advertised. PCCs must meet certain minimum data quality standards in order to participate in the Toxic Exposure Surveillance System and a variety of quality assurance checks are made when the data are edited and computerized.

The use of a standard format by different Poison Centers with standard definitions for each data element means that studies can be done using two or more centers (Veltri et al. 1987). The voluntary nature of the PCC system means that not all exposures to poisons are reported in any given catchment area served by the PCC. The extent of under-reporting is not known. More importantly, it is not known whether or how reported cases differ from unreported cases. Thus, any study using PCCs as a source for cases can only be judged representative of the universe of exposures reported to PCCs and not the entire universe of all poison exposures. PCC data is a simple form of a case series and therefore is not appropriate for complicated statistical analysis or extrapolation to the general population. However, given the large proportion of the U.S. population served by PCCs and the large number of poison exposures, factors identified within this selected series are likely to be helpful for targeting particular types of exposure situations for risk mitigation.

There is an incentive for individuals and health care providers to report cases because of the immediate service provided in the form of treatment recommendations available 24 hours a day,

365 days a year. Each Poison Center must keep records on all cases handled by the Center in a form that is acceptable as a medical record (AAPCC 1988). The standardized form that is used must contain all data elements filled out and sufficient narrative to permit peer review and medical or legal audit. These forms must be submitted to the AAPCC's Toxic Exposure Surveillance System within deadlines and meet quality requirements as specified in guidance of the AAPCC.

To participate in the Toxic Exposure Surveillance System, a PCC must be certified. To be certified a PCC must fulfill the following criteria (AAPCC 1988):

1. Have a board certified physician on-call at all times with expertise in medical toxicology.
2. Have specialists in poison information who have completed a training program and are certified by the AAPCC (once eligible for certification).
3. Maintain a comprehensive file of toxicology information sources and have ready access to a major medical library.
4. Maintain written operational guidelines which provide a consistent approach to evaluation and management of toxic exposures.
5. Have an ongoing quality assurance program including regularly scheduled conferences, case reviews and audits.
6. Keep records on all cases handled by the Center with data elements and sufficient narrative to allow for peer review.
7. Submit all case data to the Toxic Exposure Surveillance System, meet deadlines and quality requirements and include all required data elements. Taken together all these criteria help assure the quality of the data.

Examination of AAPCC annual reports from 1985 through 1994 found that 13 states had little or no coverage during most of that time period (Litovitz et al. 1986-1995). They were Nevada, Oklahoma, Texas, Arkansas, Mississippi, Illinois, Iowa, North Carolina, South Carolina, Delaware, Connecticut, Vermont, and Maine. Of the 73 reported organophosphate-related deaths reported from 1980 through 1992 (reported above), 44% occurred in these 13 states that lacked coverage by the AAPCC. This suggests that the most serious cases of poisoning may be under-represented in AAPCC data. This problem of under-reporting limits the ability to extrapolate beyond the areas served by the AAPCC.

Over-reporting may also occur when symptoms are reported over the phone which cannot be confirmed by a physician or laboratory tests for exposure or effects. Though some 25% of cases are referred to the PCC by a physician, the majority involve a phone call from the victim or relative. Poison Specialists must rely on their experience and judgment to determine which cases have

symptoms consistent with the toxicology, dose, and timing of the exposure. While some misclassification can be expected to occur from this approach, it is not expected to be differentially biased among pesticides. That is, there is no reason to believe that Poison Specialists are likely to misclassify diazinon more or less than other pesticides.

Diazinon was one of 28 chemicals for which Poison Control Center (PCC) data were requested. The following text and statistics are taken from an analysis of these data; see December 5, 1994 memo from Jerome Blondell to Joshua First.

The 28 chemicals were ranked using three types of measures: (A) number and percent occupational and non-occupational adult exposures reported to PCCs requiring treatment, hospitalization, displaying symptoms or serious life-threatening effects and (B) ratios of poisonings and hospitalization for PCC cases to estimated pounds reported in agriculture for pesticides used primarily in agriculture.

A. Occupational and Non-occupational Exposure in Adults

As part of a Data-Call-In (procedure requiring pesticide registrants to generate data or perform studies), registrants for 28 organophosphate and carbamate pesticides obtained 8-year summaries of the national database maintained by the AAPCC (Blondell 1994). The 28 pesticides were selected based on the Office of Pesticide Program's concern for acute worker poisonings, especially in agricultural settings. An examination of cases reported to the California Pesticide Illness Surveillance Program found that PCCs captured only 22% of the occupational cases reported to the state (Blondell 1996).

There were a total of 20,565 diazinon cases in the PCC data base (see Table 2). Of these, 749 cases were occupational exposure; 519 (69.3%) involved exposure to diazinon alone and 230 (30.7%) involved exposure to multiple chemicals, including diazinon. There were a total of 10,079 adult non-occupational exposures; 9060 (89.9%) involved this chemical alone and 1019 (10.1%) were attributed to multiple chemicals. Workers who were indirectly exposed (not handlers) were often classified as non-occupational cases. Information on children are described in section B. below.

Table 2. Number of exposures to diazinon in occupational, non-occupational adults, and children (0-5 years) reported to PCCs, 1985-1992.

Age/Occup. group	single*	mixed*	total	% mixed
Occupational** Adults	519	230	749	31%
Non-occupational Adults	9060	1019	10079	10%
Children 0-5 years	9219	518	9737	5%
Total	18798	1767	20565	9%

* Single: cases involving exposure to single products containing diazinon. Mixed: cases involving exposure to two or more products.

** Occupational cases are those that are a direct result of the victim being on the job or at the workplace when exposed.

In this analysis, four measures of hazard were developed based on the Poison Control Center data, as listed below:

1. Percent of all accidental cases that were seen in or referred to a health care facility (HCF).

2. Percent of these cases (seen in or referred to HCF) that were admitted for medical care.

3. Percent of cases reporting symptoms based on just those cases where the medical outcome could be determined.

4. Percent of those cases that had a major medical outcome which could be defined as life-threatening or resulting in permanent disability.

Health care facility use and hospitalization vary regionally and are subject to socio-economic factors. Therefore, these measures have drawbacks as measures of risk. Table 3 below summarize these data for diazinon exposures involving single products and compare these measures with the median for all 28 insecticides. Exposure to diazinon alone or in combination with other chemicals was evaluated for each of these categories, giving a total of 8 measures. A ranking of the 28 chemicals was done

based on these measures with the lowest number being the most frequently implicated in adverse effects.

Table 3. Measures of Risk From Occupational and Non-occupational Exposure to Diazinon Using Poison Control Center Data from 1985-1992[a]

	Occupational Exposure	Non-occupational Exposure
Percent Seen in HCF		
Single chemical exposure	57.4 (68.2)	30.8 (44.0)
Multiple chemical exposure	59.5 (69.8)	32.2(46.1)
Percent Hospitalized		
Single chemical exposure	5.7 (12.2)	9.6 (9.9)
Multiple chemical exposure	10.8 (14.3)	9.6 (12.6)
Percent with Symptoms		
Single chemical exposure	84.6 (85.8)	71.9 (74.0)
Multiple chemical exposure	87.0 (85.8)	72.9 (75.2)
Percent with Life-threatening Symptoms		
Single chemical exposure	0.3[b] (0.0)	0.2[c] (0.0)
Multiple chemical exposure	0.4[b](0.5)	0.2[c] (0.05)

a Extracted from Tables 2, 3, 5 and 6 in December 5, 1994 memo from Jerome Blondell to Joshua First; number in parentheses is median score for that category.
b The percents calculated here are based on a single case for a single chemical exposure and 2 cases for multiple chemical exposures.
c The percents calculated here are based on 10 to 12 cases.
* Top 25% of chemicals are ranked with a superscript of 1 to 7

Compared to other organophosphate and carbamate insecticides, diazinon had average or below average evidence of effects in every category except percent with life-threatening symptoms (Table 3). For occupational exposure there was only one life-threatening case involving diazinon singly and two exposures involving diazinon and other products. The number of cases is too few for comparative purposes. For non-occupational exposure, ten life-threatening cases were reported for exposure to diazinon alone and twelve life-threatening cases were reported which involved exposure to diazinon and other products. Based on these numbers 0.2 percent of the

diazinon cases (where outcome was known) had life threatening effects, a figure that ranked just above the median value for all 28 organophosphate and carbamate insecticides.

The total number of non-occupational exposures, symptomatic cases, and health care referred cases were compared to the total number of estimated products in U.S. homes and the total number of estimated applications for 10 insecticides widely used in the home (Blondell Memorandum December 5, 1994). The ratios for diazinon was slightly below the median in all cases.

B. Exposure in Children

A separate analysis of the number of exposures in children five years of age and under from 1985-1992 was conducted. For diazinon, there were 9737 incidents; 9219 involved exposure to diazinon alone and 518 involved other pesticides as well. Compared to 14 other organophosphates and carbamates that 25 or more children were exposed to, diazinon cases were as likely to be seen in a health care facility, require hospitalization, or develop symptoms. However, the 27 life-threatening cases, or 0.4 percent of the cases with known outcome represented a two-fold increase over the median value. Of the 27 cases, six were known to involve a diazinon product containing 25 percent active ingredient and one case was due to a product containing 0.5% active.

Four accidental deaths have been reported by Poison Control Centers in children due to diazinon since 1983. In 1984 two cases were reported: one in a four year old and one in a 6-12 year old. The type of product or route of exposure was not reported for these cases. In 1992, an 18-month-old boy drank an unknown amount of diazinon concentrate. In 1994 a 3-month-old was reportedly exposed to environmental residue from a diazinon ant and roach killer.

The total number of childhood exposures, symptomatic cases, and health care referred cases were compared to the total number of estimated products in U.S. homes and the total number of estimated applications for 10 insecticides widely used in the home (Blondell 1994a). The ratios for diazinon was slightly above the median when compared to number of containers in the home and the same as or slightly below the median when compared to number of applications.

Data on all oral pesticide exposures reported in children (aged less than 6 years) in 1989 were analyzed (Blondell 1994b). Out of 83 active ingredients used in pesticides, diazinon ranked 34th with a ratio of 58 cases of oral exposure per 1 million containers reported in homes. The ratio was based on a total of 918 cases of oral exposure in 1989 and an estimated 15,703,000 diazinon containers in U.S. homes in 1990 (Whitmore et al. 1992).

The median for all 83 active ingredients was 40 oral exposures per million containers. Nine of the top 10 pesticides ranked by this ratio were bait formulations which are often readily accessible to infants and young children.

V. CALIFORNIA PESTICIDE ILLNESS SURVEILLANCE SYSTEM

California is the one of only a few states that actively requires mandatory physician reporting of all occupational pesticide poisoning incidents (U.S. General Accounting Office 1993). California is unique in that its system of reporting has been in place much longer than any of the other states. Long enough, so that one can go back 20 years to determine patterns of poisoning by specific pesticide. Unlike other states, physicians treating worker compensation cases are not supposed to be paid unless a pesticide poisoning is properly reported. Many cases not covered by worker's compensation probably go unreported and some types of workers without coverage have a disincentive to see a physician.

The following excerpt from a publication by Edmiston and Maddy explains how the California pesticide poisoning reporting system works (Edmiston and Maddy 1987):

> Any physician in California who knows or has reasonable cause to believe that a person is suffering from any disease or condition caused by a pesticide is required by law to report such a case via telephone to the local health officer within 24 hrs of the initial examination. The health officer is then required to immediately notify the local County Agricultural Commissioner (CAC), and report to the CDFA and California Department of Health Services via a Pesticide Illness Report (PIR) within seven days. Once the CAC is notified an investigation of the incident is initiated to determine the circumstances of exposure.
>
> A Doctor's First Report of Work Injury . . . is sent by physicians, as required by Section 6409 of the California Labor Code, to the Division of the Labor Statistics (DLS) of the Department of Industrial Relations for any illness or injury resulting from circumstances within the workplace. The [physician's reports] are sorted by DLS staff and any case that might be related to pesticides is sent to the CDFA Worker Health and Safety Branch (WH&S). All [physician's reports] received by WH&S are screened for possible pesticide involvement; those cases potentially pesticide-related are to be sent to the appropriate CAC for follow-up investigation.

> When the investigations by CAC staff are complete, they are sent to the Worker Health and Safety Branch. An evaluation of each case is then completed as described in the section of data evaluation procedures.

The following excerpts, also from Edmiston and Maddy 1987, provide the data evaluation procedures:

> Information received from the CAC investigation, the physician's report(s), toxicological data and any other pertinent background information is used in the evaluation of each incident reported.
>
> The incidents are first evaluated as to the completeness of the information submitted. Sufficient information is needed to be able to determine the relationship between the pesticide exposure incident and the reported illness or injury. . . .
>
> Cases are classified as to the likelihood of a relationship between the reported pesticide exposure and the illness/injury occurrence. This determination is based on all available information including, but not limited to, information documenting exposure, the medical assessment, and chemistry and toxicology of the pesticide(s) involved. Each case is classified according to the following scheme: Definite; Probable--a high degree of circumstantial evidence suggesting the illness/injury was due to pesticides, but not a definite relationship; Possible--uncertain of circumstantial evidence, but some likelihood exists; Unlikely--very little likelihood of a relationship exists, but not enough information is available to exclude some chance the illness/injury was due to pesticides; and Unrelated--the incident is determined to be unrelated to pesticide exposure.
>
> The type of illness or injury reported is classified as follows: "Systemic"--the physician reports signs/symptoms indicative of internal illness such as digestive, neuromuscular or respiratory system effects; [starting in 1989 respiratory symptoms distinct from systemic disease were reported separately] "Eye"--topical injury, such as conjunctivitis; "Skin"--topical injury, such as a chemical burn or rash; and "Eye and Skin"--topical injury involving both the eye and skin.

A. Illnesses for 1982 through 1995

Detailed descriptions of 860 cases submitted to the California Pesticide Illness Surveillance Program (1982-1995) were reviewed.

In 521 of these cases, diazinon was used alone and was judged to be responsible for the health effects. Only cases with a definite, probable, or possible relationship were reviewed. Diazinon ranked 5th as a cause of systemic poisoning in California from 1990 through 1994. Table 4 presents the types of illnesses reported by year. Table 5 gives the total number of workers that took time off work as a result of their illness and how many were hospitalized and for how long.

Table 4. Cases Due to Diazinon Exposure in California Reported by Type of Illness and Year, 1982-1995

Year	Illness Type					
	Systemic[b]	Eye	Skin	Resp	Combination[c]	Total
1982	41	7	-	-	-	48
1983	40	8	4	-	-	52
1984	28	7	3	-	-	38
1985	22	5	-	-	1	28
1986	39	5	2	-	-	46
1987	24	6	2	-	-	32
1988	45	6	3	-	-	54
1989	23	6	-	2	-	31
1990	57	4	2	4	1	68
1991	15	4	3	1	2	25
1992	15	3	3	2	1	24
1993	19	4	2	-	-	25
1994	19	3	1	-	-	23
1995	17	4	2	3	1	27

Year	Illness Type					
	Systemic[b]	Eye	Skin	Resp	Combination[c]	Total
Total	404	72	27	12	6	521

[b] Category includes cases where skin, eye, or respiratory effects were also reported.
[c] Category includes combined irritative effects to eye, skin, and respiratory system.

Table 5. Number of Persons Disabled (taking time off work) or Hospitalized for Indicated Number of Days After Diazinon Exposure in California, 1982-1995.

	Number of Persons Disabled	Number of Persons Hospitalized
One day	55	7
Two days	34	8
3-5 days	28	11
6-10 days	13	4
more than 10 days	12	3
Unknown	46	14

A total of 404 persons had systemic illnesses or 77.5% of 521 persons. A total of 72 persons had eye illnesses or 13.8% of 521 persons. Only 5% of the cases involve skin injuries or illnesses. A report of all hospitalized cases in California for 1982 through 1994 ranked diazinon first as the leading cause of hospitalization. However, a third of these cases were attempted suicides or homicides. Among the accidental hospitalized cases most occurred among homeowners who misused the product or left it within the reach of very young children. Among the occupational cases that were hospitalized there were four applicators, three of whom were applying the product by hand. A variety of worker activities were

associated with exposure to diazinon as illustrated in Table 6 below.

Table 6. Illnesses by Activity Categories for Diazinon Exposure in California, 1982-1995

Activity Category	Illness Category					
	Systemic[b]	Eye	Skin	Resp	Combination[c]	Total
Applgrou	16	5	3	-	-	24
Applhand	48	39	4	3	3	97
Applother	4	-	-	-	-	4
Clean/Fix	-	1	-	-	-	1
Coinciden	17	2	1	-	-	20
Driftexp	30	2	1	1	1	35
Emerresp	3	-	-	1	-	4
Expotoco	29	3	1	2	1	36
Flagger	-	1	-	-	-	1
Manuform	-	1	-	-	-	1
Mixload	5	4	1	-	-	10
Other	7	-	-	-	-	7
Pack/Proc	-	-	1	-	-	1
Resifield	2	4	5	-	-	11
Resiother	1	-	-	-	-	1
Applnon	6	1	-	1	-	8
Resistru	73	1	3	3	-	80

Activity Category	Illness Category					
	Systemic[b]	Eye	Skin	Resp	Combination[c]	Total
Driftnon	8	-	1	-	1	10
Nonoccb	76	2	1	-	-	79
Resinon	3	-	-	-	-	3
Othernon	76	6	5	1	-	88
Total	404	72	27	12	6	521

[a] Applgrou= ground applicator; Applhand= applicator, hand-held spray/dust equipment; Applnon= non-occupational application exposure; Applother= applicator, other spray/dust application methods; Clean/Fix= cleaning and/or repairing pesticide contaminated equipment; Coincidental= coincidental; Driftexp= exposure to pesticide that has drifted from intended targets; Driftnon= non-occupational exposure to drift; Emerresp= emergency response personnel; Expotoco= persons handling pesticide products between packaging and end-use; Flagger= aircraft flagger; Manuform= manufacturing/formulation plant workers; Mixload= mixer and/or loader of pesticide concentrates and dilute pesticides; Nonoccb= other non-occupational exposure; Other= other occupational exposure; Othernon= non-occupational miscellaneous exposure; Pack/Proc= packing, processing, or retailing commodities; Resifield= field worker exposed to residue in the field; Resinon= non-occupational residue exposure; Resiother= worker exposed to residue neither agricultural nor structural; Resistru= worker exposed to residue of structural treatment

[b] Category includes cases where skin, eye, or respiratory effects were also reported

[c] Category includes combined irritative effects to eye, skin, and respiratory system

Nearly half of the diazinon exposures reported in California involve workers, mostly in agricultural settings. Those who apply diazinon by hand were at greater risk than any other category, accounting for 38% of the occupational categories. This is also the category responsible for over one-half of the adverse effects to the eyes. Drift exposures and persons handling product in transport or in warehouses combined to account for over a quarter of the remaining occupational cases. Detailed review of the occupational cases found that lack of protective equipment was involved in at least 19 incidents. Equipment failure (e.g., hose breaks) was a factor in at least 26 cases. And inadequate precautions when cleaning or maintaining equipment were involved in

at least 12 cases.

Non-occupational categories (the last six categories listed in Table 6) accounted for just over half of the total cases and 60% of the systemic cases. Thirty percent of the non-occupational cases resulted from residues left from structural applications. By far the majority of these cases occurred when occupants reentered a structure that had just been sprayed. One of the most serious cases of this type involve 35 people who got sick when a carpet was improperly treated. Bystanders were present during the application and affected in at least 20 of these cases. There were even a few cases where the outside of a building was treated and people inside claimed exposure and illness. Earlier summaries prepared by California for the years 1975 through 1982 examined all pesticide illnesses involving workers exposed to drift or residue indoors (CDFA 1976-1982). Of the 471 systemic illnesses reported during this six year time period, 123 (26%) were due to diazinon, more than for any other pesticide. In 1979, 57 workers were affected in a single incident when they reentered their offices which had not been adequately ventilated.

A total of 18 of the California cases occurred as a result of suicide attempts. Not surprisingly, they accounted for a significant portion of the cases that were hospitalized. Accidental ingestions in children or adults, when stored in an improper container, was another important source of the more serious hospitalized cases.

One particularly serious case in 1992 involved a five-week-old baby who became very ill (vomiting, diarrhea, foaming at the mouth, pinpoint pupils, labored breathing, crying, irritable) less than 24 hours after a unlicensed structural pest control operator treated counter tops, the ceiling, and other areas in the home. This case was confirmed by severe inhibition of the cholinesterase. Other cases that suggest that very young infants may be in danger from residues of diazinon include two three-week-old twins hospitalized with symptoms of rapid, shallow breathing, profuse nasal and bronchial secretions, and pinpoint pupils (English et al. 1970). However, only one of the twins exhibited slightly reduced pseudocholinesterase and none of the other family members (including a two-year-old) exhibited signs of illness. A fatal case in a three-month-old who was exposed to residue from a misapplication (puddles were visible on the floor) was reported by the American Association of Poison Control Centers in 1994 (Litovitz et al. 1995). The infant was found dead in its crib so the symptoms in this case are not known. Also, there was no cholinesterase test or other verification, so this can only be considered a possible case. Another case involving a three-month-old infant is discussed below by Wagner and Orwick (1994). This

case also involved excessive application of diazinon inside the home.

B. Ratios of poisoning

The incidence of **systemic poisoning cases** in agricultural workers reported to the California was compared to the number of applications of diazinon. Those calculations, along with the median score for a total of 29 pesticides, are presented in the Table 7.

Table 7. Systemic Poisonings/1,000 Applications in Selected Agricultural Workers Exposed to Diazinon in California, 1982-1989[a]

Pesticide	Number of Appl.	Poisonings/1,000 Appl. (N) Primary Pesticide Only			Poisonings/1,000 Appl.(N) Multiple Pesticide Exposure		
		Handlers	Field Workers	Total	Handlers	Field Workers	Total
Diazinon	61,351	.21 (13)	.20 (12)	.41 (25)	.49(30)	.62 (38)	1.11 (68)
Median		.21	.20	.41	.44	.50	1.02

a Extracted from Table A5 in December 5, 1994 memo from Jerome Blondell to Joshua First; number in parentheses is the observed number of poisoned cases.

Diazinon had the ratios for handlers and field workers (poisonings per 1,000 applications) that matched the median for 29 insecticides used widely in California when exposures to mixtures were excluded (See Table A5 in the December 5, 1994 memo.) The ratios were slightly higher when mixtures were included.

The total number of poisoning cases related to structural pest control applications is clearly excessive when compared to the extent of use. From 1990 through 1994 California reported 74 systemic poisonings due to diazinon where a structural pest control operator (PCO) was involved in the application (Mehler 1997). This was 16 percent of the 466 cases where a structural PCO was involved and the individual pesticide responsible for the poisoning could be identified. A nationwide survey of residential and commercial PCO use estimated 180,000 pounds active ingredient of diazinon applied indoors compared to a total of 9,232,000 pounds active ingredient for all pesticides used indoors (Lucas et al. 1994). Thus, diazinon accounted for only two percent of indoor use but account for 16 percent of the systemic poisonings, a eight-fold increase in risk.

VI. NPTN

On the list of the top 200 chemicals for which National Pesticide Telecommunications Network received calls from 1984-1991 inclusively, diazinon was ranked 3rd with 1598 incidents in humans reported (7.3% of the total) and 248 incidents in animals (5.6%, mostly pets). From 1984 through 1990, NPTN received 1,022 calls complaining of unusual sensitivity to pesticides; multiple chemical sensitivity (MCS) in most cases. Diazinon was the second ranked pesticide for which there were 104 MCS type complaints or 10% of the total, though it only accounts for 5% of the use in the home. (Whitmore et al. 1992).

VII. LITERATURE REVIEW

There are numerous case reports of diazinon poisoning in the scientific literature. No attempt will be made to review all of the cases reported here. Rather selected reports suggesting new or different health effects and reports permitting dose-response assessment will be presented.

In a review of animal and human toxicology, Gallo and Lawryk (1991) noted that a wide variation in response had been observed to different batches of diazinon. In at least some cases, presence of sulfotepp or monothio-TEPP have been implicated (Soliman et al., 1982). For example, two spray men in Egypt were using back sprayers with inadequate protection and were poisoned by a formulation with these contaminants in 1979. Evidence has shown, at least in formulations from decades past, that these more toxic transformation products can be produced as diazinon breaks down over time. Current formulation practices are designed to reduce this problem to a minimum.

Gallo and Lawryk (1991) reported on three-week old twins who developed shallow breathing, nasal and bronchial secretions and pinpoint pupils after their apartment had been sprayed with 1% diazinon using “approved” application methods. Gallo and Lawryk commented that this case appeared to be a rare example of illness due to respiratory exposure with little or no inhibition of cholinesterase. This may be partly because normal levels of cholinesterase are approximately 20-30% lower in children under the age of four months when compared to adults (Karlsen et al. 1981). However, two other reports suggest that poisoning symptoms can occur without cholinesterase inhibition. Nine inmates in a correctional facility in Alabama accidentally drank a homemade alcoholic beverage which contained diazinon (Kessler and Mracek 1973). The beverage was made from oatmeal, sugar, molasses, and raisins and allowed to ferment. Diazinon concentrate, mistakenly thought to be another product that would mask the odor of the fermenting brew, was placed on top of the plastic bag with the brew

and apparently leaked through. Each of the nine prisoners drank at least one-half pint of the brew. All nine developed symptoms and eight of the nine had cholinesterase values that were low but still within the normal range. Only one inmate had cholinesterase levels that were clearly below normal. A more recent report from Israel (Richter et al. 1992) concerns a family of four who developed symptoms which include vomiting, sleep problems, fatigue, dizziness, headache, and chest heaviness. Urine samples were positive for diazinon exposure but only slight depressions were seen in serum cholinesterase measurements. The authors report that persistent household exposure to residues were the most likely explanation for the health complaints. Ten days after a thorough wash down of the apartment, family members were free of symptoms and urine levels of diazinon metabolites were below detection. These studies strongly suggest that cholinesterase measurements may not always be a reliable indicator of significant exposures that can lead to poisoning symptoms.

Relatively small dermal exposures to diazinon have been hazardous. The most extreme example in the literature involved an application of just one teaspoonful to the genitals of a 58 year old male to treat a pubic lice infection. This case developed life-threatening symptoms of coma and seizure, but recovered with aggressive treatment. The authors note that absorption is likely to be very high (near 100%) across the thin skin of the scrotum based reports by Maibach et al. (1971). Assuming that 25% diazinon was used, the dose from 1 teaspoon in a 70 kg man would be 18 mg/kg body weight (5,000 x .25/70). Hayes (1963) reported on three cases that applied 80 mg of diazinon to the skin (in a 1% solution) and all three were poisoned (doses around 1 mg/kg). The unusually low dose which led to a coma in one of the three cases is inconsistent with other reports and may be due to earlier formulations of diazinon transforming into more toxic TEPP and sulfotepp (Gallo and Lawryk 1991). Two female gardeners at a nursery in Singapore accidentally knocked over a container of diazinon that spilled on one of them and they both cleaned up the splash without taking precautions or changing out of their contaminated clothing (Lee 1989). The most heavily exposed woman experienced diarrhea, dizziness, cyanosis, frothing at the mouth, drowsiness, and pulmonary edema and had to be put on a respirator. She later developed acute pancreatitis which was attributed to the effects of the exposure to diazinon. Several other reports in the literature have associated diazinon or other organophosphate insecticides with the development of pancreatitis (Lee 1989, Dagli et al. 1981).

A more recent concern of organophosphate poisoning and diazinon poisoning in particular is the development of an intermediate syndrome characterized by extreme muscle weakness. This muscle weakness, which is usually reported 1-4 days after the

exposure, can lead to paralysis of the limb and neck and respiratory muscles, requiring mechanical ventilation (Hall and Baker 1989, Samal and Sahu 1990, Sheth et al. 1995). Most of the reports of this syndrome have involved suicidal ingestions of potentially lethal doses.

Wagner and Orwick (1994) reported development of persistent hypertonicity in a three month old infant that persisted to eight months of age. Overall muscle tone was increased in the arms and legs with evidence of hyperreflexia, closed hand posture, and hyperextension when rolling over. At eight months of age the home was found to have had an excessive application of diazinon five weeks prior to the onset of symptoms. Diazinon had been applied as a 1% solution in a broadcast manner over the interior of the family's home by an unlicensed applicator. Cholinesterase levels in the infant were normal but urine measurements were positive for diazinon exposure. Six weeks after the infant left the home, muscle tone returned to normal. Wagner and Orwick (1994) suggest that other neurotoxic effects of diazinon rather than simple cholinesterase depression may have been responsible for this case.

Another effect of organophosphate poisoning suggested in some studies is pancreatitis (Weizman and Sofer 1992). Weizman and Sofer conducted a prospective study of 17 children seen in a hospital for organophosphate or carbamate poisoning. All cases had signs and symptoms compatible with poisoning and reduced levels of plasma cholinesterase. Five of the children subsequently developed pancreatitis as measured by serum trypsin. The clinical manifestations were relatively mild, abdominal pain being the primary gastrointestinal symptom. One of the children with pancreatitis had been poisoned by diazinon. The authors concluded that pancreatitis is not rare in anticholinesterase intoxication. Others have also reported cases of pancreatitis due to diazinon (Lee 1989, Dagli et al. 1981).

There is one report in the literature of a patient developing severe poisoning while working in his yard for two days which had been treated with diazinon (Kurt 1988). In this case it was postulated that he was unusually susceptible to the effects of diazinon on account of the medication he was taking for high blood pressure (cimetidine). However, this increased susceptibility has been questioned and no similar reports have been forthcoming (May 1989).

Older surveys have been conducted which measured mortality and morbidity nationwide. Hayes and Vaughn (1977) reported that for five years surveyed (1956, 1961, 1969, 1973, and 1974), diazinon was responsible for 12 deaths due to accidental causes. Diazinon ranked fifth as a cause of death for these five years, accounting

for three percent of all accidental deaths related to pesticides. A survey of hospitalized pesticide poisonings in a six percent sample of the nation's hospitals estimated 123 non-occupational cases and 10 occupational cases per year over the six year period 1977-1982 (Keefe, Savage and Wheeler 1989). In this survey of hospital records, the identity of the specific pesticide was unknown in 32% of the cases, so the actual number of diazinon hospitalizations was probably somewhat higher. Diazinon ranked second as a cause of non-occupational cases and 12th as a cause of occupational cases in this hospital study. These rankings are primarily due to the widespread use of diazinon. A survey of home use by EPA in 1976-1977 found that diazinon was the seventh most common pesticide present in the home (Savage, Keefe and Wheeler 1980). A more recent survey conducted in 1990 found that diazinon was the ninth most common pesticide (excluding disinfectants) present in 15.8% of all households (Whitmore et al. 1992). There was an estimated 18 million applications indoors and 57 million applications outdoors in the year prior to this survey based on respondent's recollection.

Reichart et al. (1977) reported on two families where eight children were poisoned from eating contaminated oatmeal in Hawaii. The homes where the children lived had received repeated applications of undiluted 25% diazinon concentrate for control of roaches. It is not known whether the children may have had reduced cholinesterase from dermal exposure to treated surfaces. The prepared oatmeal was found to contain 58 parts per million diazinon. Assuming 100 grams of oatmeal were ingested and that the children (aged 5-10) weighed on average about 25 kg, then the estimated dose that caused poisoning would be 0.23 mg/kg. In a case reported in Michigan an 18 month old boy was accidentally fed "roach milk" which was analyzed to contain 0.5% diazinon (Detroit News, November 29, 1985). The boy was taken to the hospital in coma, but recovered with treatment. Assuming he weighed 11.3 kg (average weight of 18 month old) and ingested 8 ounces of formulation (227 grams), the dose received would have been 100 mg/kg. This dose may be considered a low lethal dose for children, given the life-threatening symptoms reported.

Zwiener and Ginsburg (1988) reported on 37 cases of severe toxicity in young children in Texas from organophosphates and carbamates. Five of the 37 (14%) were due to diazinon; all from ingestion of improperly stored containers and confirmed by markedly reduced cholinesterase. One of the five cases experienced respiratory arrest from ingestion of an illegal "roach milk" product similar to the case described in Michigan (Ginsburg personal communication). This two-year-old patient reportedly developed encephalopathy and seizure disorder secondary to the mechanical ventilation required to save his life.

Gallo and Lawryk (1991) report that a dosage of 0.02 mg/kg was a no-effect level in adult volunteers. Two men who ingested five doses over five days had marked inhibition of plasma cholinesterase at a dose of 0.025 mg/kg/day. However, it should be noted that these tests were reported back in 1967 when the type of manufacture and formulation may have significantly increased toxicity.

Miller and Mitzel (1995) examined 37 cases of multiple chemical sensitivity associated with organophosphate or carbamate exposure. Nine of these 37 (24%) were due to diazinon; a number exceeded only by chlorpyrifos with 19 cases (51%).

Epidemiologic studies of workers exposed but not poisoned

An extensive behavioral evaluation was performed on 46 pest control workers with short-term, low-level exposure to diazinon (Maizlish et al. 1987). Workers were tested before and after applying diazinon as part of their work for the state. Fifty-three (53) controls were selected from supervisors or workers at a second site engaged in pest detection or inspection of agricultural commodities. Each subject completed a brief neurological screening examination, a symptom questionnaire, and computer-assisted tests of concentration, eye-hand coordination, pattern recognition, visual memory, and finger tapping. The authors reported that behavioral effects were not demonstrated in this study:

> Comparisons between exposed and non-exposed groups showed minor deficits of performance among the exposed, particularly post-shift Symbol-Digit speed and Pattern Memory accuracy. While applicator versus non-applicator differences are not readily explained, diazinon exposure is probably not responsible because poorer performance was not observed in more powerful analyses of dose-response.

The estimated whole body exposure to diazinon in this study was characterized as low, estimated to be 1.5 mg diazinon per day. The average duration of exposure for this group of workers was 39 days with a range from 17 to 67 days, again relatively short compared to other studies.

One important confounder reported by the authors was healthy worker selection. This confounder occurs when affected individuals leave the workplace or select-out of exposed jobs as a result of the adverse effects they develop. Other problems reported with the study included a relatively low response rate especially among older males. Selection bias, subject motivation and observer/subject bias were also potential sources of error. Despite these problems this study does provide evidence that short-term, low-level exposure is not likely to produce chronic neurobehavioral effects. This finding is supported by three

additional studies, reviewed below, which were not limited to cases exposed to diazinon.

A study by Ames et al. (1995) examined neurobehavioral function in 45 male subjects with documented cholinesterase depression but not frank organophosphate poisoning. Subjects were selected from medical monitoring records maintained in California for those who apply organophosphate or carbamate insecticides and undergo routine cholinesterase testing. Workers with a 30% decline in red blood cell cholinesterase or a 40% decline in plasma cholinesterase were eligible to be removed from work and could be candidates for this study. The identity of the pesticide responsible for the decline in cholinesterase was not known. This study was part of another study which looked at poisoned subjects (Steenland et al. 1994). Ninety (90) controls were selected from among the friends that were brought either by subjects with cholinesterase depression in this study or friends of subjects in the study of poisoned cases. A number of factors including age, ethnicity, weight, grade level, and language of test were identified as potential confounders and adjusted for in the analysis. A total of 27 tests were administered including 10 tests of nerve conduction, 2 tests of vibration, 7 neurobehavioral test, 5 tests of mood, and 3 tests of motor coordination. Subjects who had experienced cholinesterase depression did not score significantly worse on any of these tests.

A cross-sectional study of 67 Hispanic farmworkers and 68 gender-, age-, ethnicity-, and education-matched controls was performed in Washington State (Engel et al. 1998). Exposed subjects were apple thinners who did not have any previous history of handling pesticides in the previous six months or any history of pesticide poisoning. The apple thinners were primarily exposed to azinphosmethyl and possibly to phosmet or methyl parathion. Controls were recruited from local workplaces including sewing factories, food processors, fruit-packing houses, recreational areas, and restaurants. Unlike the study by Ames et al. described above where all subjects were male, 43% of the exposed subjects in this study were female due to over sampling in this group. Cholinesterase levels were taken and were slightly, but significantly lower in the exposed group. The exposed workers did not perform significantly worse on eight nerve conduction tests. When analyses were restricted to thinners, no significant dose-response relationship was observed between hours involved in thinning and any neurophysiological measure. Note that no tests were performed on neurobehavioral function such as memory, concentration, or mood. The authors concluded:

> The results indicate that OP pesticide exposure during a growing season at the low levels observed in these workers was not related to detectable impairment in peripheral nerve

conduction or neuromuscular function.

In contrast to the study described above which was limited to neurophysiological measures, the study reported by Fiedler et al. (1997) was limited to neuropsychological performance. In this study, 57 male tree fruit farmers were compared with 42 age-matched cranberry/blueberry growers and hardware store owners (unexposed). Subjects were selected from a mail survey to self-employed tree fruit farmers who were also licensed pesticide applicators in two counties in New Jersey. Only 39% of those contacted by mail agreed to participate in the study, identified as a farmers' health study. Of the 84 who agreed to participate, 27 were excluded due to advancing age (7), little or no exposure to pesticides (4), other illness (4), and scheduling conflicts (12). For the control group, letters were sent to 237 blueberry/cranberry growers who were expected to have little or no exposure to pesticides. However, only 34 (14% response rate) agreed to participate and 12 of these were not eligible for the reasons given above. To augment the size of the control group, 285 hardware store owners were contacted from the same community. Of these, only 22 (8% response rate) agreed to participate from which 20 were actually tested. In summary the control group consisted of 22 blueberry/cranberry growers and 20 hardware store owners. Detailed exposure history was taken by questionnaire which focused on number of acres treated with organophosphates for each year of farming and type of handling (e.g., mixing, airblast application, etc.) and use of protective equipment. The examination included a detailed medical history, a complete physical examination with focus on neurologic function (e.g., cranial nerves, sensation to light touch, deep tendon reflexes, and gait), and a neuropsychological test battery which included measures of concentration, visuomotor skills, memory, expressive language, and emotional distress. All farmers were tested for red blood cell cholinesterase to confirm they were free from recent acute exposures. None of the farmers had a history of pesticide poisoning. Because subjects and controls differed significantly on years of education and reading test scores these factors were included in the analysis. Simple reaction time (a measure of concentration) was significantly slower in the exposed group. However, no other significant differences were seen on measures of visuomotor skills, memory (visual or verbal), or emotional distress as measured by MMPI scales (e.g., depression, introversion). Given the large number of comparisons reported in this study the finding for slower reaction time may be due to chance. The authors concluded:

> the present study in conjunction with the literature on organophosphates, suggests that absent an acute poisoning episode, demonstrable neurobehavioral performance deficits in an asymptomatic population are at most subtle and often not associated with symptoms . . . Therefore, prevention of acute

poisoning may be the most important strategy to reduce the likelihood of significant cognitive deficits resulting from long-term use of organophosphates.

Based on the four studies that did not include potentially poisoned workers, including one study specific to diazinon, the Health Effects Division concludes that available evidence does not support a finding that low-level exposure to organophosphates, or diazinon in particular, can cause chronic neurological or neurobehavioral effects in the absence of poisoning.

Epidemiologic studies of poisoned workers

Two types of studies have been conducted to assess chronic neurological and neurobehavioral effects of organophosphate poisoning: cases series and case-control studies which are considered below.

Case Series

Gershon and Shaw (1961) reported on 16 workers with 1-10 years duration of exposure to organophosphates. These 16 workers are not a representative sample of workers, but a selected group. Assessment of psychiatric symptoms revealed that 8 had impaired memory, 7 depression, 6 impaired concentration, 5 had schizophrenic reactions, 4 had irritability, and 4 had persistent headaches. Lack of controls and sampling methodology prevent concluding that the symptoms seen in this case series were necessarily due to the chronic exposure or poisoning from organophosphates.

Metcalf and Holmes (1969) examined two datasets based on workers involved in the manufacture of organophosphates. The first dataset examined 56 exposed workers and 22 controls. The OP exposed workers exhibited more forgetfulness (53% of exposed versus 20% of controls), visual difficulty (30% versus 0%), general fatigue (35% versus 5%), muscle aches and pains (12% versus 0%) and difficulty thinking (12% versus 5%).

Their subsequent study of the same workforce included psychological testing, electroencephalograms (EEG), and a neurological examination. The authors reported that the exposed group demonstrated "disturbed memory and difficulty maintaining alertness and appropriate focusing of attention" from the psychological testing. Direct interviews of these workers with multiple or severe exposures elicited complaints of being slowed down, less energetic, and having more memory difficulty and irritability than the minimally exposed workers. Neurological

tests did not show differences between highly and minimally exposed workers on tests of sensory or motor deficits. The EEG examination was conducted on all workers in the study and did show changes. These changes were characterized as "a minimal type of EEG disturbance, but it mirrors, to a lesser degree, the more severe EEG disturbances seen after acute exposure".

Both this study and the earlier one by Metcalf and Holmes (1969) are marred by a lack of description of the sources of cases and controls, lack of case definition, absence of statistical testing for significance, and lack of any discussion of possible biases or confounders. Due to these deficiencies, the study must be treated more as a case series than as a controlled epidemiologic study. This means that the findings can be characterized only as suggestive or supportive of the results from other studies.

Holmes and Gaon (1957) examined 600 patients who were factory workers with exposure to organophosphates, principally parathion and TEPP. In this survey 25 or 4 percent reported symptoms of irritability, nervousness, fatigue, lethargy, memory impairment, confusion, decreased mental concentration, and various problems with muscle aches and pains including sensations of numbness and weakness in the limbs. These persistent symptoms occurred "in the more severe exposures and in those with multiple exposures".

In one case of severe exposure to an organophosphate, Holmes and Gaon (1957) recorded the patients subsequent mental confusion in the patient's own words: "Get tired--hard to breathe--short of breath, just like I'd run up a hill. This usually happens when I do anything that requires some energy--(fast walking--short runs, etc.). Had a couple of restless nights--nervous. I still get quite nervous--lot more irritable than before. Very absent-minded since last exposure. My mind seems to like to wander--quite marked. I cleaned out garage just after the exposure and now I don't know where I put half the stuff. I distinctly remember trying to store it in places where I could remember, but now I have to go through all the stuff to find it. It was 2 weeks sometimes before I found what I wanted. My thinking seems rather flighty--I've been fairly good in arithmetic, but can't do it too well in my head now. Can't concentrate on more than one thing at one time".

Two physicians in California examined 114 OP poisoning cases 3 years afterward to look for chronic effects (Tabershaw and Cooper 1966). They originally sought 235 subjects that had OP poisoning in 1960, but only 114 were located, examined and included in the final analysis. Of the 114 cases, 6 were classified as severe (coma or convulsions present, hospitalized an average of 8 days), 54 were considered moderate based on clinical notes, and 54 were considered mild (patient remained ambulatory or recovered rapidly

from limited therapy). Nearly half, 53 cases required hospitalization. In 6 individuals visual disturbances were reported which the patients insisted had not been present before the poisoning episode and which they attributed to the poisoning. Another 7 patients complained of persistent headaches. Five poisoning victims complained of nervousness or irritability. Notably 22 of the 114 workers (19%) reported they could no longer tolerate smelling or contacting pesticides. Of the 22, 16 had given up work involving contact with pesticides because of their intolerance and six continued to work on the farm but avoided contact as much as possible. One wonders how many of the 61 poisoned workers that could not be located for this study may have left because of persistent symptoms or intolerance (i.e., healthy worker selection). Other studies attempting to measure such effects may miss recruiting affected individuals because they have left pesticide-related work after being sensitized. A controlled epidemiologic study would be needed to confirm the results identified in this report of a case series.

Hirshberg and Lerman (1984) collected data on 236 case records of organophosphate and carbamate poisoning from 8 hospitals in Israel from 1958 to 1979. OP poisoning was confirmed by laboratory evidence of cholinesterase depression. Carbamate poisoning was confirmed by unequivocal evidence of direct exposure. Only 5 cases of carbamate poisoning were included. Accidental exposure accounted for 89% of the cases and 26 or 11% were attempted suicides by oral ingestion. According to the authors: "Depression, confusion, and agitation were noted in nine patients after recovery from the acute phase of poisoning. Other complaints were insomnia and motor weakness without objective neurological deficits". Seven of these 9 cases were considered to have only mild poisoning based on their clinical symptoms. All of the 9 cases had been poisoned by organophosphates.

Controlled epidemiologic studies

The studies by Savage et al. (1988), Rosenstock et al. (1991), and Steenland et al. (1994), presented below, are examples of high quality epidemiologic studies. A study by Savage et al. (1988) in Colorado and Texas examined 100 cases poisoned by organophosphates and 100 matched controls for neurological and neuropsychological function. Controls were matched on age, sex, race, ethnic background, education, and occupational class. Significant differences were found on tests of memory, abstraction, depression, and mental impairment. On average the exposed subjects were poisoned 9 years before testing. Poisoned subjects scored significantly worse on 4 of 5 summary scores of psychoneurological function and on 18 of 34 subtests. Among the tests that poisoned subjects scored worse on were the Wechsler Adult Intelligence

Scale, logical analysis, abstract reasoning, verbal fluency, problem solving, concentration, sensitivity to social stresses, and fine motor coordination and speed. Relatives of the 100 poisoned subjects and controls were questioned about psychological function in 22 areas. Statistically significant differences were found in four areas, depression, irritability, social withdrawal, and confusion. Again, the controls performed better in these areas than the case group.

It was not possible from this single study to state that organophosphate poisoning leads to adverse effects on psycho-neurological function. A number of potential sources of bias, particularly selection factors may have affected the results of this one study. However, results from this study have been replicated on poisoned workers in Nicaragua and again in California.

Rosenstock et al. (1991) performed a retrospective cohort study of agricultural workers in Nicaragua who had been hospitalized with organophosphate poisoning. Of 52 eligible patients hospitalized over a two year period, 38 men were located, and 36 agreed to participate in the study. Controls were a close male friend or sibling from the same community who had never been treated for pesticide poisoning and was no more than 5 years different in age from the case participant. Both members of the pair (case and control) were examined during May-June 1989 before the onset of the 4-5 month spraying season. Six of the seven tests from the World Health Organization core neurobehavioral test battery were administered, along with a brief symptom inventory, 6 additional Spanish-translated tests, and a 16 item self-reported symptom inventory. These tests were administered an average of 2 years after the time of hospitalization for a poisoning.

Poisoned workers scored significantly worse on five of the six WHO core neurobehavioral tests, 3 of the 6 Spanish-translated tests, and the 16 item self-reported inventory. Deficits were noted in auditory and visual attention, visual memory, visuomotor skills, steadiness and dexterity. These findings replicated, to a large degree, those of Savage et al., which is an important consideration when judging the weight of evidence for a conclusion that OP poisoning is a cause of chronic neurobehavioral effects.

Steenland et al. (1994) studied chronic neurological sequelae in 128 workers poisoned by organophosphates between 1982 and 1990 and 90 controls. The poisoned group performed significantly worse on measures of sustained visual attention and mood. If the poisoned group was restricted to those with documented cholinesterase inhibition or those who had been hospitalized, the poisoned subjects also showed poorer performance on vibrotactile

sensitivity tests. This study concluded "The evidence of some long-term effects of poisoning is consistent with two prior 7studies."

This study had certain limitations common to many epidemiologic studies. However, these limitations do not effect the conclusion. The 128 poisoned cases were only 31% of the 416 potential participants sought for the study. Of the remainder 37% could not be located, 19% could not be contacted (mailings sent to their listed address were not responded to), and 13% refused to participate. Some of the individual were excluded from some or all of the tests. The first 16 individuals examined did not receive the test for mood which was added after the first round of testing. Eighteen subjects could not take the neurobehavioral tests primarily because of inability to read. Thirty-eight of the poisoned cases (30%) failed to bring a friend to serve as a control for the study. One disadvantage of the use of friends as controls is that they might be selected by the cases on the basis of similarities in mood and other personality factors under study that would tend to prevent discovery of significant effects.

Unlike the two earlier case-control studies, this report attempted to determine whether effects were associated with exposure to particular organophosphate insecticides. Diazinon as a primary cause of poisoning was not associated with adverse effects, however, only 11 subjects were available for study. In 19 cases where diazinon was a source of exposure but not the primary cause of poisoning there was some evidence of more tension on mood scales. The Steenland et al. (1994) study mentions in their introduction that a subset of organophosphates may cause delayed-onset peripheral neuropathy by effects on the neuropathic target esterase, a property not shared by other organophosphates. No similar mechanism is suggested as to why in the current study some organophosphates and not others would effect either the peripheral nervous system or the central nervous system. All of the organophosphates under study poison primarily by their ability to inhibit the cholinesterase enzyme. Both central and peripheral nervous systems may be affected. Therefore, if chronic effects are brought about by depression of neural and brain cholinesterases, then such effects can be expected from any organophosphate insecticide.

A neurological and a psychoneurological study were performed on the same group of farmers that use organophosphate sheep dip in the United Kingdom. Though not well characterized in these two studies, sheep dipping is generally a messy process that can easily lead to poisoning symptoms. A study by the Veterinary Products Committee (1996) showed considerable evidence of symptomatic cases though almost none were documented with cholinesterase testing or

other medical documentation. Therefore, although these two studies are grouped with studies of workers who have been poisoned, this categorization of exposure is questionable at best. Though not specified in either study, the principal organophosphates used for dipping sheep in the United Kingdom are diazinon, propetamphos, and chlorfenvinphos (Veterinary Products Committee 1996).

The neurological study was limited to 20 sheep farmers and 10 quarry workers selected from the main cohorts of 146 sheep farmers and 143 quarry workers (Beach et al. 1996). The sheep farmers were selected based on a symptom questionnaire administered 24 hours after dipping sheep. The 10 farmers with the highest symptom scores were selected along with the 10 farmers with the lowest symptom scores. The unstated assumption is that reporting lots of symptoms immediately after exposure is a good means to identify those who have experienced chronic effects. A more meaningful approach would have been to identify those workers who complain of the more typical chronic symptoms reported in studies of individuals who had been poisoned and months or years later complained of persistent headache, blurred vision, muscle weakness, problems with memory, concentration, confusion, irritability and depression. By choosing the two extremes, the authors of this study have assured that their study population is not typical of the cohort of 143 exposed farmers. A hallmark of chronic symptoms is that they are not a function of recent exposure. Therefore, the classification scheme used is inappropriate. No comment is made in the study about how the 10 quarry workers were selected, other than that they came from a single study site. This implies that selection may have been based on a convenience sample and not well-matched to the study population of farmers. Quarry workers average 8 years younger than the study groups but this difference was not significant. This is primarily due the small sample size and does not rule out age as a possible confounder in this study. The study found no difference between groups for cranial nerve abnormalities. Thirteen types of measures were used to assess the motor system (e.g., reflexes, calf circumference, muscle power, gait, and reflexes) and only one statistically significant difference was found for calf circumference which was lower in the more symptomatic farmers. Sensory examination included fine touch, vibration, joint position sense, and two point discrimination. The only statistically significant finding was for two point discrimination on the hands and feet. The authors concluded that “a clear relation was not found between exposure and the neurological abnormalities detected within groups of farmers.” They note that this may be partly due to the relatively crude measures of exposure and the fact that individual susceptibility may determine who gets effects. Though their findings did not easily fit into a pattern of neurological disease, the authors argue that either subclinical episodes of intoxication or long term

low level exposures may have led to the significant differences that were observed:

> they suggest that some neurological changes, albeit relatively subtle, had occurred as a consequence of long term exposure to organophosphate sheep dip at concentrations which had never induced sufficient symptoms that medical attention was sought.

In the neuropsychological study of the same cohort of farmers testing was done at least two months after the last dipping to avoid testing for acute effects (Stephens et al. 1995). For this study the entire cohort of 146 farmers and 143 quarry workers (controls) were used. Letters were used to recruit every tenth farmer from the Wool Marketing Board list of sheep farmers, but only resulted in a response rate of 33%. Subsequently, telephone contacts were made which produced a response rate of 69%. The overall response rate for quarry workers was 35%. Farmers differed significantly from quarry workers on a number of potentially confounding factors. Farmers were older, had lower alcohol consumption, less computer familiarity, and were less likely to have English as a first language than the quarry workers. So these factors were included as potential confounders in the analysis. Lack of recent exposure to organophosphates in the farmers was verified by urinalysis for dialkylphosphates. Farmers performed significantly worse than controls on 3 of 8 psychological tests: Symbol Digit Substitution; Syntactic Reasoning; and Simple Reaction Time. These effects remained after adjustment for the confounders. Farmers apparently reported more symptoms suggestive of psychiatric disorder, however, these symptoms were not analyzed individually. Tests of short-term memory and learning were not significantly different between the two groups as might have been expected based on earlier studies.

The authors concluded that:

> chronic effects on the nervous system have occurred in this group of farmers and that these effects are likely to be associated with long-term exposure to organophosphates. These effects are subtle in nature, and although identifiable with sensitive neuropsychological tests, they are unlikely to be manifest as clinical symptoms. The results do suggest, however, the need to reduce exposure to organophosphates as far as possible.

Levin et al. (1976), and in a separate report, Rodnitzky et al. (1975) examined 11 farmers and 13 commercial applicators. Farmers tested prior to the spraying season and farmers not involved in pesticide application were used as controls and matched on sex, age, and education. While no significant differences were seen on neurobehavioral tests, there was some increased anxiety in commercial applicators. In order to participate in the study, pesticide applicators had to have been exposed in the past two

weeks to organophosphates. Therefore, this study tested for immediate neurobehavioral effects of exposure and has no bearing on long term neurobehavioral effects of poisoning or exposure. The study may have been confounded by selecting farmers as controls who did have neurobehavioral deficits as a result of previous exposure (more than two weeks ago) or even poisoning to organophosphates. Therefore, these studies are not relevant to a review of chronic neurobehavioral effects of organophosphate poisoning.

Weight-of-Evidence Conclusion for poisoned workers

The studies presented above do provide surprisingly consistent results of neurobehavioral damage due to organophosphates. While the association is not especially strong, it is fairly specific and has been found in a variety of different populations. Evidence of the direct effects of organophosphates on the brain mean the effects observed may be considered biologically plausible. Alternative explanations such as chance, bias, and confounding are less likely explanations for the associations seen in these studies than exposure to organophosphates.

Taking these case series and case-control studies together, it now appears reasonable to conclude that some subset of organophosphate poisoned subjects probably experience persistent neurobehavioral effects. This finding has been supported by other authors (Karalliedde and Senanayake 1989, U.S. Congress, Office of Technology Assessment 1990, World Health Organization 1990). A review by Karalliedde and Senanayake (1989) came to a similar conclusion: "Behavioral changes have been documented following acute or chronic OP poisoning. These symptoms may take months to regress. In human subjects exposed to OP agents to an extent sufficient to depress plasma or erythrocyte [red blood cell] cholinesterase, some or all of the following observations have been made: (1) Impairment of vigilance, information processing, psychomotor speed and memory. (2) Poor performance and perception of speech. (3) Increased tendency to faster frequencies and higher voltages in EEG records." Ecobichon's 1994 review of organophosphates and neurological disease concluded "Sufficient anecdotal information can be found in the medical literature to signify that there are persistent and serious complaints lasting from 6 months to several years and, possibly, forever."

The World Health Organization (1990) suggests that 5 percent of occupational poisonings due to organophosphates result in these effects. The Office of Technology Assessment of the U.S. Congress (1990) has arrived at a similar conclusion: "The pesticides parathion, mevinphos (Phosdrin), and malathion are frequently reported as causing health problems. Case reports and studies of acute poisonings of agricultural and other workers indicate that 4

to 9 percent of the acutely poisoned individuals experienced delayed or persistent neurological and psychiatric effects." These effects include "irritability, depression, mood swings, anxiety, fatigue, lethargy, difficulty concentrating, and short-term memory loss. These symptoms may persist for weeks and months after the initial exposure." Given the results from controlled studies by Savage et al. (1988), Rosenstock et al. (1991), and others listed above this last sentence can be changed to read: "These symptoms may persist for months or years after the initial exposure."

Table 8. Results from key studies supporting a relationship between organophosphate poisoning and chronic neurobehavioral effects.

Reference	study type	Latency	Symptoms
Case series Gershon and Shaw 1961	16 OP cases	1-10 years later	8 had impaired memory, 7 had depression, 6 impaired concentration, 5 schizoid, 4 headache, 4 irritability.
Metcalf and Holmes 1969	56 OP cases	6 years average	disturbed memory, difficulty in maintaining alertness, irritability, visual difficulty, muscular aches and pains.
Holmes and Gaon 1957	600 OP cases	?	increased irritability, marked forgetfulness, confusion in thinking, inability to concentrate.
Tabershaw and Cooper 1966	114 OP cases	3 years later	7 persistent headaches, 6 visual disturbances, 5 nervousness and irritability, 22 chemically sensitive.
Hirshberg and Lerman 1984	236 OP cases	after acute poisoning	9 depression, confusion, and agitation.
matched case-control studies Savage et al. 1988	100 cases and controls	9 years later on average	case performed poorer on: academic skills, motor skills, abstraction, flexibility in thinking, memory, depression, irritability, withdrawal, confusion.

Rosenstock et al. 1991	36 cases and controls	2 years later on average	cases performed poorer on: auditory and visual attention, visual memory, visuomotor skills, steadiness, dexterity.
Steenland et al. 1994	128 cases and 90 controls	5 years later on average	cases performed poorer on: visual attention and mood (confusion and tension).
Stephens et al. 1995	146 cases and 143 controls	based on exposure rather than poisoning	cases performed worse on sustained attention and speed of information processing.

Most often reported effects

Irritability
Memory impairment
Inability to concentrate
Confusion
Depression

Reported in two or more studies

Visual disturbances
Persistent headaches
Muscle aches and pains
Fatigue
Psychomotor impairment
Nervousness

VIII. SUMMARY AND CONCLUSION

Diazinon is one of the leading causes of acute insecticide poisoning incidents in the United States. This finding is based largely on an examination of Poison Control Center reports. Much of this frequency is accounted for by the widespread use of this chemical inside and outside the home. Not counting synergists, diazinon was the fifth most common insecticide found in U.S. homes in a survey conducted by EPA in 1990 (Whitmore et al. 1992).

Generally, the rate of poisoning for diazinon does not differ greatly from that for other cholinesterase-inhibiting insecticides. In California the rates per thousand applications for diazinon were very close to the median value for 29 selected insecticides. Similarly in the Poison Center data the ratios of symptomatic cases to measures of home use (number of containers or applications) for diazinon was close to the median. However, when organophosphates as a group are compared to other pesticides, a different picture emerges.

Organophosphates are responsible for disproportionately more serious poisonings than other pesticides. In the 1990 survey of home and garden use (Whitmore et al. 1992, page 55 and Table G) 19% of the containers in U.S. homes were organophosphates. In the 1993 survey of non-agricultural pesticide use by certified and commercial applicators, 21% of the pounds active ingredient applied were organophosphates (Lucas et al. 1994, Table 13). Similarly, for Poison Control Centers, 15% of all unintentional pesticide exposures are due to organophosphates, but 18% of the symptomatic cases, 27% of the hospitalized cases, and 28% of the life-threatening or fatal cases were due to organophosphates (based on 1993-1996 data provided by AAPCC). National death statistics report that 40% of the accidental deaths from pesticides (where the type of pesticide is known) were due to organophosphates during the 1980s (Blondell 1997). A similar pattern is seen in agriculture in California, where information is collected on both agricultural use and poisoning, organophosphate insecticides account for just 5% of the use (in pounds active ingredient for 1990-1994), but account for 30% of the systemic pesticide poisonings in agricultural settings (230 cases during the same time period, data provided by the California Pesticide Illness Surveillance Program). Thus, the excess risk from organophosphates for agricultural uses is six times (30/5) higher than would be expected given the percent use.

By examining existing reporting systems and various usage patterns, certain types of use appear to pose greater health risks while other types of use are associated with little or no significant health impacts. This finding may be biased by problems with surveying certain user groups (e.g., agricultural

fieldworkers). Available limited data suggest that incidence of human poisonings associated with agricultural use of diazinon are comparable to other insecticides. The one exception to this appears to be hand applications in both agricultural and non-agricultural settings which often result in poisoning and eye injury to the applicator. Additional surveys of poisoning would be desirable to confirm this finding.

The main concern with diazinon appears to be structural applications by homeowners or Pest Control Operators (PCOs) both indoors or outdoors and the availability of highly concentrated products which can cause life-threatening poisonings in children. According to California data incidents, involving structural application by a Pest Control Operator are eight times more likely with diazinon than with other pesticides used by PCOs. Based on anecdotal reports of ingestions, it appears that doses in the range of 350-400 mg/kg may be lethal in humans. Several life-threatening cases have been reported when young children were exposed to 25% diazinon concentrates. The number of homes and applications involving PCOs is needed to better understand the population at risk. This information would help determine the incident rate, the primary measure of risk.

Most of the more serious poisonings appear to involve misuse, especially improper dilution, application to inappropriate sites (e.g., carpet), failure to use minimal protective equipment (eye protection, appropriate and proper fitting respirator), and failure to take precautions when performing routine maintenance of equipment or cleaning up spills. A surprisingly large number of incidents occur when bystanders such as building or home occupants remain in the immediate vicinity during application or when they reenter a recently treated structure. At least 20 of the well-documented California cases involved bystanders present during application and at least 80 cases (35 in a single incident) involved reentry into a recently treated structure. Some of these reentry cases were due to improper dilution or treatment of inappropriate surfaces. In some cases it appears symptoms are brought on by the offensive odor of the compound. It should be recognized that individuals developing symptoms brought on by odor effects are poisonings by definition. Cholinesterase depression, though a useful indicator for exposure, does not have to be present to prove that poisoning has occurred. If odors are offensive enough to cause illness and to seek medical attention, then the circumstances that lead to such morbidity should be examined so that risk reduction measures can be identified and implemented.

IX. RECOMMENDATIONS

1. A prospective epidemiologic study or statistically valid survey is recommended for the purpose of determining the extent (how common or rare), circumstances (intensity, duration, and type of exposure), and persistence and severity of chronic health effects. Study subjects should be those who experience acute adverse effects both with and without evidence of cholinesterase depression. Health effects to be surveyed include chronic neurobehavioral effects, symptoms of peripheral neuropathy, and multiple chemical sensitivity. Children under age six must be included in this study and a registry developed to follow poisonings involving infants until they are old enough to take sophisticated neurobehavioral tests.

2. The Health Effects Division recommends that registrant-sponsored training and education programs be developed and implemented for PCOs using diazinon around homes and other structures where people are likely to be present. Training should focus on how to perform proper dilutions, what surfaces are appropriate to treat, and proper maintenance of spray equipment to avoid failures that result in accidental exposure.

3. Indoor home and office uses should be considered for cancellation whether by homeowners or Pest Control Operators. Certain exceptions may be considered if the following measures can be introduced and fully enforced: Labels for indoor use (both homes and offices) should specify that other persons not involved in the application (e.g., office workers, children) should not be in the immediate vicinity during application. In the case of prisons, hospitals and other institutions arrangements to transport potentially sensitive persons away from the immediate vicinity of the application may be needed until sprays have dried or ventilation has reduced the odor. After application, thorough ventilation should be required and a reentry period before occupants are allowed to reenter the treated area.

4. Labels should be amended to specify rates of application and minimum application intervals. Application rates and intervals should be based on efficacy and toxicity to humans and pets.

5. All applicators should be required to use proper eye protection when applying diazinon by hand. Labels should warn about use of protective equipment when performing routine maintenance or when cleaning up spills.

6. A pamphlet should be given to homeowners describing the application, advising on precautions, health effects including symptoms of adverse reactions, potential routes of exposure, protective measures for young children, what to do and who to contact in the event of a spill or other accident is recommended.

Input from EPA, state regulatory agencies, university extension, and other interest groups should be solicited and the pamphlet field tested before being distributed.

7. HED recommends that consumers not be permitted to handle highly concentrated diazinon products intended for structural or residential application indoors or most outdoor uses. A single swallow from the 25% concentrate can lead to life-threatening poisonings or deaths as evidenced by data for Poison Control Centers. All diazinon products should be in child-resistant packaging because serious cases have occurred even with products with the lowest percent active ingredient. Any products more than 10% concentrated should be considered for cancellation because of the risk of fatality in children. Paint additives containing 87% diazinon available in small container are especially hazardous and should be removed from consumer use as soon as feasible. One way to limit the risk to young children is to permit only larger size containers that would be harder for children to pick up. For example, certain outdoor concentrates would be permitted, but only for containers larger than 1 quart. Such instances should be well-justified and involve the minimum percentages of active ingredient practical.

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